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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,747	04/24/2007	Martin Andrew Crockard	06-346	5890

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EXAMINER	
POPA, ILEANA	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/595,747	CROCKARD ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 4 and 6-13 have been cancelled. Claims 1-3 and 5 have been amended. Claims 1-3 and 5 are pending and under examination.

2. All rejections/objections pertaining to claims 4, 8, and 9 are moot because the applicant cancelled the claims in the reply filed on 06/04/2010.

The objection to claim 5 as being in improper form is withdrawn in response to the amendment filed on 06/04/2010.

Claim Rejections - 35 USC § 112, 1st paragraph - enablement

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-3 and 5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. Factors to be

considered in determining whether a disclosure meets the enablement requirement of 35 USC § 112, first paragraph, have been described by the court in *In re Wands,* 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skills of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided.

The presently amended claims are drawn to a method for the detection of the presence or the risk of breast cancer in a patient by detecting the expression of the gene set forth by SEQ ID NO: 1 (i.e., DD20) and other known breast cancer markers in a sample isolated from the patient. The instant specification teaches by exemplification using differential display to identify differences in the gene expression profiles between excised breast tumor tissue and samples from adjacent, co-excised normal breast tissue, wherein one of the identified genes is DD20 set forth by SEQ ID NO: 1 and wherein DD20 comprises a putative, small ORF encoding a product with unknown function. The above evidence has been noted and considered. However, the instant specification is not enabled for the present claimed invention for the reasons discussed below.

The Nature of the Invention

The claimed invention is drawn to using genetic tests to detect the presence or the risk of cancer in a patient. The nature of the claimed invention requires a robust and reliable correlation between the level of expression for the claimed markers and the presence of breast cancer in the tested subjects. While the art may teach a good correlation for the known breast cancer markers, there is no such correlation for DD20. Thus, although one of skill in the art would know that known breast cancer markers could be used to detect the presence or the risk of breast cancer, the instant invention is not drawn to using known breast cancer markers alone. The instant invention requires the presence of DD20 as a breast cancer marker and there is no reliable correlation between the level of DD20 expression and the presence of breast cancer in the tested subjects. Hence, from the nature of the invention, one of skill in the art would not reasonably predict that DD20 could be used as a marker for breast cancer.

The State of the Prior Art and the Level of Predictability in the Art/Amount of Experimentation Necessary

At the time the invention was made, and even in the present, using differential display to identify genes relevant to cancer was known to be unpredictable. While determining the level of any particular transcription product is routine, correlating any compared level with a particular phenotype is unpredictable. The art teaches that, although differential display experiments could identify genes whose expression is altered in particular diseases, it is not clear which of the many identified genes will be confirmed as risk factor.

The specification contemplates to use DD20 to diagnose cancer or the risk of cancer. However, both the specification and the art fail to confirm DD20 as a risk factor for cancer. In the absence of such a confirmation, it is not clear how DD20 could be used in diagnosis methods. Just because differential display experiments identify a significant increase/decrease in the expression level of a particular gene in a particular disease does not mean that this gene could be used to diagnose the disease. Henry et al. (The Oncologist, 2006, 11: 541-552) teach:

> "[t]he marker is only useful if the estimate of its magnitude is reliable and reproducible. In this regard, many investigators conclude that their marker of interest has clinical utility if in their study the difference in outcomes between marker "positive" and marker "negative" patients is less than conventional measures of statistical significance ($p<.05$). This conclusion may be mistaken. Statistical significance only suggests that in the population chosen for that study, the difference observed are likely not to be a result of chance alone. It does not imply clinical utility, nor does a $p\text{-value}<0.05$ document the validity of the tumor marker. Although it is important to determine that the differences in outcome achieve statistical significance, statistical significance alone does not determine clinical utility."

Along these lines, the art teaches that, although microarray experiments demonstrated that LIM expression level was significantly increased in the brains of schizophrenic subjects, LIM was not confirmed as a risk factor for schizophrenia (see Kato et al., Molecular Psychiatry, 2005, 10: 1045-1055, Abstract, p. 1053, column 2). The art also teaches that: **(i)** mRNA levels can be affected by the presence of SNPs in the regions complementary to the probes used, wherein expression change thought previously to be significant, was actually due to a SNP not properly detected in the array (see Sliwerska et al., Biol. Psychiatry, 2007, 61: 13-16; Abstract, p.14, column 1 and Figure 1); **(ii)** gene expression experiments performed with tumor samples could lead to false positives/negatives because of the quality of the available tissue, for example

samples from patients treated with anti-cancer medication which can alter gene expression (see Simon et al., European Journal of Cancer, 2008, 44: 2707-2713, p. 2709, column 1, first full paragraph); and **(iii)** results from experiments using tumor tissue to identify biomarkers have little value for early detection (i.e., detection of the presence or of the risk of cancer) because they are related to changes that occur a long time after the initiation of cancer (see Baker, J. Natl. Cancer Ins., 2009, 101: 1-4, p. 1, paragraph bridging columns 1 and 2).

Therefore, it is unpredictable that a gene identified by differential display as having modified expression levels could serve as a marker for the detection of the presence or the risk of cancer in patients. The observed increased DD20 expression level could be due to any of the above factors. The specification does not demonstrate otherwise. The mere identification of DD20 as being upregulated in a differential display experiment is not evidence that DD20 is a risk factor for cancer such that it can be used to detect the presence or the risk of cancer.

Given these teachings, one of skill in the art would not know *a priori* and would require undue experimentation to determine whether determining DD20 expression level would result in successful detection of the presence or of the risk of cancer in patients.

The Amount of Direction or Guidance/The Existence of Working Examples

Given the complexities associated with the nature of the claimed invention, one of skill in the art would have to turn to the specification for guidance.

Apart from the disclosure that a significant increased DD20 expression was detected in breast tumor samples, the instant specification fails to provide the necessary demonstration that DD20 is a risk factor for cancer. Neither the art nor the specification demonstrates that DD20 expression can be used to detect cancer or the risk of cancer.

Furthermore, the results presented in Fig. 2 and 3 demonstrate that DD20 could be also expressed at the same levels in normal tissues isolated from the same patients or that some breast tumor tissues do not express DD20 at all. Therefore, even with increased DD20 expression level in some samples, it is still unclear that this increased expression is a reliable and specific indicator for detection of breast cancer or the risk of breast cancer.

The specification does not provide the guidance or the working examples required to overcome the art-recognized unpredictability of detecting the presence or the risk of cancer by using the expression levels of a single gene identified as being upregulated in tumor tissues. The art does not provide the guidance necessary such that one of skill in the art would be able to practice the claimed invention.

Conclusion

In conclusion, the instant specification do not appear to reasonably render the claimed invention as a whole patentable under 35 USC, 112, first paragraph. As such, the specification fails to teach one of skill in the art how to overcome the unpredictability of using the instantly claimed method.

The applicant argues that the presently amended claims are fully enabled as the detection of DD20 expression in combination with known biomarkers of breast cancer increases the specificity of such methods (in addition to allowing further characterization of breast tumors). More specifically, the invention as presently claimed does not involve the identification of a single biomarker, such as DD20, but rather involves detecting the presence of a known biomarker plus a further biomarker (DD20). Moreover, it is also noted at the final paragraph of page 12 of the application that DD20 compares favorably with some of the most highly regarded "standard" breast cancer markers, such as ERα and c-ErbB-2, as evident in the expression distribution of both sets of markers in sample breast tissue. In other words, the methods of the present invention accurately diagnose the presence or risk of breast cancer on the basis of at least one known biomarker but, in addition, utilization of DD20 enables the method to more accurately diagnose the presence or risk of breast cancer, and may provide further information on the type of breast cancer and the stage of the disease. The effectiveness of DD20 in aiding in the diagnosis of the presence or risk of breast cancer would be clear to one of skill in the art in view of the specification and the demonstrated similar expression patterns of DD20 to known breast cancer biomarkers.

The applicant's arguments are acknowledged; however, they are not found persuasive for the following reasons:

The art clearly teaches that enhanced expression identified by differential display does not equal clinical utility (see the rejection above). Furthermore, just because a the expression of gene compares favorably with some of the standard breast cancer

markers in RT-PCR does not mean that the gene is a breast cancer marker. Expression of other genes compares favorably with the standard breast cancer markers in RT-PCR; however, not all of these genes are breast cancer markers. To be considered a marker, a gene must be validated as a marker, i.e., a correlation between the gene and breast cancer must be provided. The instant specification only discloses that, after further necessary analysis, DD20 may prove to be a marker (see p. 12). However, the instant specification fails to provide the necessary analysis, i.e., the instant specification does not provide a reliable correlation between DD20 and breast cancer. The art does not provide such a correlation. Clearly, further experimentation is required to establish if DD20 could be considered a breast cancer marker and this experimentation is undue. Based on the lack of guidance in the specification and the art, one of skill in the art would not recognize that DD20 has utilities as a breast cancer marker, either by itself or in combination with other markers. Thus, one of skill in the art would not recognize that adding DD20 would improve the accuracy of the methods already known and used in the prior art or that using DD20 would provide further information on the type of breast cancer and the stage of the disease. For these reasons, the rejection is maintained.

Conclusion

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ileana Popa/
Primary Examiner, Art Unit 1633